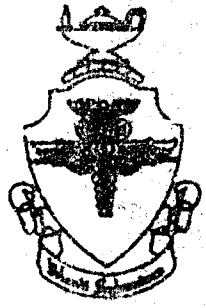
PHARMACODYNAMICS OF A RADIOPROTECTIVE DRUG: 2-(1-DECYLAMINO)ETHANETHIOSULFURIC ACID

JOSE A. MARTINEZ-O'FERRALL, Major, USAF, MC
GEORGE S. MELVILLE, JR., Lieutenant Colonel, USAF



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FOREWORD

This study was carried out in the Radiobiology Division under task No. 775703 and partially under subtask 5710-RMD 3068, DASA (STMD). The work was performed between February and May 1968. The statistical data were analyzed by the Biometrics Division. The paper was submitted for publication on 20 February 1969 to fulfill the research requirement of phase II of the Residency in Aerospace Medicine.

The assistance of Horace E. Hamilton in preparing the report is gratefully acknowledged.

The animals involved in this study were maintained in accordance with the "Guide for Laboratory Animal Facilities and Care" as published by the National Academy of Sciences–National Research Council.

This report has been reviewed and is approved.

Jo M Quashnock

JOSEPH M. QUASHNOCK
Colonel, USAF, MC
Commander

ABSTRACT

One phase of the search for radioprotective agents is the study of the physiologic and pharmacologic mechanisms responsible for toxic and protective effects. In this study, the drug 2-(1-decylamino)ethanethiosulfuric acid (WR-1607) was injected, according to different dosage schedules, into control and irradiated *Macaca mulatta* monkeys. Changes in hemograms and blood chemistries were measured, and clinical observations were recorded. The response in control animals appeared to be that to a temporary chemical challenge with prompt recovery within one week. In the irradiated animals, the response corresponded to a subacute radiation syndrome. In this experiment, WR-1607 failed to mobilize physiologic mechanisms for protection again radiation injury. Further investigation of this drug as a radioprotectant should consider a different approach in method of administration.

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I. INTRODUCTION

The increasing use of atomic energy with its potential hazard of exposure of man to high dosages of ionizing radiation has generated the search for chemical preparations possessing protective characteristics against radiation injury. Testing the ability of such chemical agents to reduce lethality in irradiated experimental animals is one phase of the endeavor to obtain practical methods for modification of radiation injury. Another phase of the scientific effort is the study of physiologic and pharmacologic mechanisms responsible for the toxic and protective effects of the radioprotective agents.

The compound 2-(1-decylamino)ethanethiosulfuric acid (WR-1607), developed by the Walter Reed Army Institute of Research, has been tested in mice with promising results—50% to 90% protection in doses of 5 mg./kg. (1). Results in initial studies with dogs have not been so encouraging. Toxicity studies in rhesus monkeys have been few (2). The potential use of this drug as a radioprotective agent requires prior consideration of its pharmacodynamics. In the present study an attempt was made to evaluate the physiologic effects of WR-1607 in primates, in conjunction with a recent investigation of the radioprotective effectiveness of the compound (3). The parameters selected for evaluation were: (1) clinical picture, (2) hemograms, and (3) blood chemistries.

II. MATERIALS AND METHODS

Adult *Macaca mulatta*, ranging in weight from 6.5 to 9 lb., were used in this investigation; all but 2 were males. The primates were screened for evidence of existing disease and acclimatized for 2 weeks. They were caged individually in air-conditioned quarters and maintained as described by Young et al. (4). The 28 primates were randomly distributed

TABLE I

Experimental groups

Group	Number of animals	Drug dosage (mg./kg.)	Pre-irradiation interval (hr.)*	Radiation dose
A_1	4	10	1	Sham
A_2	4	20	1	Sham
B_1	5	10	1	850 R
B_2	5	10	3	850 R
C_1	5	20	1	850 R
C_2	5	20	3	850 R

*Time interval between drug administration and irradiation period.

into six groups as presented in table I. In addition, each irradiated group included 1 radiation control (irradiated but not administered drug) to confirm lethality of the radiation dose. No clinical, chemical, or hematologic studies were performed on the radiation controls.

The compound WR-1607, obtained from the Walter Reed Army Institute of Research, was dissolved in warm Carbowax just before injection. The concentrations were adjusted so that each animal received approximately 3 ml. of solution. The dissolved drug was administered intraperitoneally by use of standard procedures.

Whole-body irradiations were performed with a Maxitron-300 machine at a dose rate of 18 ± 2 R/min., for a total dose of 850 R.

Hematologic data were obtained by the methodologies described by Wintrobe (5).

The clinical evaluation presented in this paper is limited to body weights and rectal temperatures (tables II and III); a more extensive clinical evaluation of the compound WR-1607 in *Macaca mulatta* is available (3).

Data on the following 14 variables were collected pretreatment and on days 1, 3, and 7 postinjection:

Leukocytes
Hematocrit
Platelets
Lymphocytes
Neutrophils
SGOT
SGPT
Alkaline phosphatase
Bilirubin (direct)
Bilirubin (total)
Total protein
Albumin
Sodium
Potassium

For each variable the mean values for each time and for each group are shown in tables IV through XVI.

One-way analyses of variance were computed from the baseline data for each variable in order to check for differences between the groups before treatment. Since the animals

TABLE II

Mean weight (%) by days postinjection for irradiated and sham-irradiated primates

Group	Baseline (lb.)	Weight as percent of baseline								
		Day 3*	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28	Day 30
A_1	7.5	98†	91	95	93	93	95	92	91	93
A_2	7.2	99	88	89	94	93	89	86	86	83
B_1	6.9	100	101	96	93	81	82	83	82	77
B_2	7.0	101	97	101	90	—	—	—	—	—
C_1	6.7	102	89	93	85	—	—	—	—	—
C_2	6.9	97	101	94	99	100	80	88	89	87

In group B_1, survival ratio at day 3 was 4/5; at day 7, 2/5; at day 21, 1/5; and at day 30, 1/5.

In group B_2, survival ratio at day 17 was 0/5.

In group C_1, survival ratio at day 17 was 0/5.

In group C_2, survival ratio at day 7 was 5/5; at day 10, 2/5; at days 14, 17, and 21, 1/5; and at day 30, 1/5.

*Days after drug administration.

†Percent = group mean weight/mean baseline weight.

TABLE III

Mean rectal temperature (in degrees Farenheit) of irradiated and sham-irradiated primates

Group	Baseline	Day 3*	Day 7	Day 10	Day 14	Day 17	Day 21	Day 24	Day 28	Day 30
A_1	102.9	101.6	102.0	102.1	102.3	102.2	102.2	99.8	100.6	102.6
A_2	102.6	101.5	103.3	102.2	102.2	102.3	102.2	99.3	101.5	101.5
B_1	102.4	102.6	102.2	102.5	101.4	102.8	102.0	104.4	101.0	101.2
B_2	102.6	103.1	101.8	102.6	99.1	—	—	—	—	—
C_1	103.0	102.3	100.3	102.3	102.1	—	—	—	—	—
C_2	102.5	102 7	102.7	102.0	101.8	102.6	100.0	101.4	102.2	103.2

See table II for survival data.

*Days after drug administration.

TABLE IV

Change in leukocytes with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	7,800	17,500	9,700	10,800
A_2	8,200	11,600	12,500	11,900
B_1	8,700	10,800	1,700	600†
B_2	10,900	11,900	5,300	400
C_1	8,600	11,800	900	600†
C_2	9,100	16,700	1,400†	600‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE V

Change in hematocrit with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	42	44	38	36
A_2	40	40	34	33
B_1	40	37	35	35†
B_2	42	39	37	36
C_1	42	45	37	36†
C_2	43	44	40†	40‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE VI

Change in platelets with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	380,000	371,000	128,000	434,000
A_2	401,000	427,000	91,000	390,000
B_1	453,000	269,000	201,000	88,000†
B_2	346,000	213,000	186,000	53,000
C_1	350,000	92,000	77,000	24,000†
C_2	124,000	123,000	100,000†	43,000‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE VII

Change in lymphocytes (%) with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	75	19	64	63
A_2	66	11	50	46
B_1	78	10	38	0†
B_2	71	10	31	0
C_1	65	5	3	0†
C_2	69	4	12†	0‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

were randomly assigned to the treatment groups, no differences would be expected between the group means. As indicated in table XVII, only the leukocyte data gave a statistically significant ($P < .05$) difference between group means. It seems reasonable to assume that this difference was due to random variation only and did not reflect any bias in the way in which the animals were handled.

An analysis of variance of repeated measurements was computed for the postinjection data for each pair of groups (A_1 and A_2; B_1 and B_2; C_1 and C_2). This provided a test (G x T) of whether the response curves for the two groups in each pair were the same. It also provided tests of whether the group means (averaged over time) were the same, and whether the means (averaged over groups) for the three postinjection times (1, 3, and 7 days) were the same. These latter tests are generally meaningful only if the G x T test is not significant ($P > .05$). The probability levels for these tests are given in table XVII.

TABLE VIII

Change in neutrophils (%) with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	23	81	36	35
A_2	32	89	48	50
B_1	25	90	62	0†
B_2	29	89	67	0
C_1	34	95	17	0†
C_2	30	95	38†	0‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE X

Change in SGPT with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	34	66	34	30
A_2	31	55	32	19
B_1	25	40	29	24†
B_2	34	48	33	34
C_1	32	52	31	22†
C_2	41	42	26†	19‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE IX

Change in SGOT with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	36	110	43	53
A_2	33	118	39	43
B_1	37	35	44	30†
B_2	39	96	42	37
C_1	38	112	48	28†
C_2	40	96	34†	29‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

TABLE XI

Change in alkaline phosphatase with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	13.0	12.3	9.4	10.6
A_2	10.5	8.8	8.6	9.3
B_1	13.4	10.3	8.1	8.9†
B_2	10.5	9.2	12.8	7.6
C_1	13.1	17.0	7.7	8.3†
C_2	12.1	13.0	7.3†	6.3‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

A combined analysis was done on the data of groups B_1, B_2, C_1, and C_2. This analysis provided tests for the following: 10-mg. dosage as compared to 20-mg.; 1-hour preirradiation interval versus 3-hour interval; 1-day versus 3-day versus 7-day postinjection measurements; and interactions among these variables. The tests which were significant ($P < .05$) are indicated in table XVIII. The standard deviations for comparing means within and between treatment groups for each variable are given in table XIX. Each variable is discussed separately below.

III. RESULTS

Hemogram

Values for leukocytes, hematocrit, platelets, and relative lymphocytes and neutrophils are presented in tables IV through VIII. The values are the means for the survivors at the time of testing.

Leukocytes showed an initial increase in all animals. The initial leukocytosis was more

TABLE XII

Change in bilirubin (direct/total) with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	0.10/0.13	0.18/0.30	0.20/0.40	0.15/0.38
A_2	0.10/0.13	0.10/0.15	0.18/0.52	0.25/0.40
B_1	0.12/0.16	0.16/0.30	0.16/0.20	0.13/0.33†
B_2	0.14/0.20	0.14/0.28	0.16/0.24	0.12/0.22
C_1	0.12/0.16	0.10/0.18	0.10/0.20	0.13/0.20†
C_2	0.12/0.14	0.10/0.[illegible]	0.10/0.38†	0.20/0.30‡

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 3/5.

TABLE XIII

Change in total protein with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	7.0	7.6	6.8	7.0
A_2	6.9	7.1	6.8	7.0
B_1	6.9	6.5	6.6	6.6†
B_2	7.1	6.7	6.5	7.1
C_1	7.0	6.9	6.5	7.1†
C_2	7.0	6.8	7.0†	7.2‡

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 3/5.

TABLE XIV

Change in albumin with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	4.0	4.0	3.3	3.6
A_2	4.0	3.8	3.3	3.4
B_1	4.0	3.6	3.5	3.3†
B_2	4.0	3.6	3.3	3.6
C_1	4.1	4.2	3.6	3.7†
C_2	4.1	4.3	3.9†	3.6‡

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 3/5.

TABLE XV

Change in sodium with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	154	158	155	156
A_2	153	160	160	154
B_1	149	151	152	146†
B_2	147	152	153	146
C_1	158	154	149	149†
C_2	159	149	155†	144‡

*Time postinjection.
†Survival ratio 4/5.
‡Survival ratio 3/5.

significant for the drug-control groups. By the 3d day posttreatment the drug-control group was returning to the baseline while the irradiated animals were developing severe leukopenia as in untreated, irradiated monkeys.

TABLE XVI

Change in potassium with WR-1607 and radiation

Group	Baseline	Day 1*	Day 3	Day 7
A_1	4.8	4.2	4.9	4.8
A_2	4.8	4.1	4.7	4.6
B_1	5.2	4.2	4.5	4.2†
B_2	5.0	4.2	4.5	4.6
C_1	4.6	4.4	4.6	4.8†
C_2	5.4	3.9	5.2†	5.1‡

*Time postinjection.

†Survival ratio 4/5.

‡Survival ratio 3/5.

A significant decrease in hematocrit can be seen from day 1 to days 3 and 7. Some differences appeared in the response between groups C_1 and C_2, and the B groups responded differently from the C groups.

Platelets exhibited a decrease by day 1 in the B and C groups, and by day 3 in the A groups. The combined analysis of the B and C groups shows that the decrease developed more quickly in the C groups than in the B groups. By the 7th day the drug-control groups had returned to the baseline while the irradiated groups continued into severe thrombocytopenia.

Lymphocyte percentages dropped in all groups in the first 24 hours; those of groups A and B then recovered, but those of the heavily treated group C decreased to levels too low to count. The drug-control group recovered by the 7th day while the lightly treated group B continued into severe lymphopenia.

TABLE XVII

Probability levels in the analyses of variance

Variable	Baseline	A_1 vs. A_2			B_1 vs. B_2			C_1 vs. C_2		
		G	T	G x T	G	T	G x T	G	T	G x T
Leukocyte	< .05	< .01	< .001	NS	NS	< .001	NS	NS	< .001	NS
Hematocrit	NS	< .1	< .001	NS	NS	< .01	NS	NS	< .001	< .05
Platelets	NS	NS	< .001	NS	< .025	< .001	NS	NS	< .01	NS
Lymphocytes	NS	< .1	< .001	NS	NS	< .001	NS	NS	NS	NS
Neutrophils	NS	< .1	< .001	NS	NS	< .001	NS	NS	< .001	NS
SGOT	NS	NS	< .001	NS	NS	< .001	NS	NS	< .001	NS
SGPT	NS	NS	< .001	NS	NS	< .025	NS	NS	< .001	NS
Alkaline phosphatase	NS	NS	NS	NS	NS	< .025	< .005	NS	< .005	NS
Bilirubin (direct)	NS	NS	NS	NS	NS	NS	NS	< .1	< .001	< .025
Bilirubin (total)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Total protein	NS	NS	< .001	< .05	< .05	< .025	NS	NS	< .1	NS
Albumin	NS	NS	< .001	NS	NS	< .1	NS	NS	< .025	NS
Sodium	NS	< .025	< .025	< .1	NS	< .001	NS	NS	< .1	< .1
Potassium	NS	NS	< .001	NS	NS	NS	NS	NS	< .1	NS

Neutrophils increased in all groups within the 1st day. By the 3d day, those of group C had dropped to extremely low levels. Group B neutrophils returned to baseline levels by the 7th day, and those of group A approached the baseline level.

Manifestations in the hemograms of the irradiated-and-treated animals were comparable to the results from irradiation alone (6).

Blood chemistries

An immediate increase in SGOT and SGPT occurred in all groups, followed by a significant return to baseline by the 3d day posttreatment and postirradiation (tables IX and X). One exception appeared on day 7 when the level of SGPT for C groups fell significantly below baseline levels.

The alkaline phosphatase values showed no significant variations through the 7-day period for the A groups, but the levels were significantly below baseline at days 3 and 7 for the C groups, and at day 7 for the B group (table XI).

The total bilirubin showed an increase in all groups lasting through the 7-day period while the direct portion showed a lasting rise in only the treated, nonirradiated group (table XII); however, the evidence for any real change in either direct bilirubin or total bilirubin was very weak. Rough nonparametric evaluations showed no significant effects.

There appeared to be little consistency in the total protein response between the groups; thus it is difficult to find an interpretable pattern. An initial decrease was seen in albumin

TABLE XVIII

Significant sources of variation from analyses of B and C groups combined

Variables	Significant sources of variation
Leukocytes	T
Hematocrit	A, T, A x B x T
Platelets	A, A x B, T, A x T
Lymphocytes	A, T, A x T
Neutrophils	T
SGOT	T
SGPT	T
Alkaline phosphatase	T, A x T, B x T
Bilirubin (direct)	A x T
Bilirubin (total)	—
Total protein	B, T
Albumin	A, T
Sodium	T
Potassium	—

T = Time means.

A = Ten vs. 20 mg. drug.

B = One hr. vs. 3 hr. preirradiation.

TABLE XIX

S.D. of means within and between treatment groups for each variable*

Variables	Within	Between
Leukocytes	3,460	3,540
Hematocrit	1.92	3.04
Platelets	87,400	101,300
Lymphocytes	10.9	10.9
Neutrophils	19.0	19.0
SGOT	21.9	22.4
SGPT	11.7	16.7
Alkaline phosphatase	2.26	2.51
Bilirubin (direct)	.0897	.1093
Bilirubin (total)	.305	.386
Protein	.358	.375
Albumin	.241	.313
Sodium	3.33	3.68
Potassium	.573	.622

*S.E. of the difference between two means = S.D. $\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}$, where N_1 and N_2 are the number of observations in each mean. Comparisons within a group should be made only where $N_1 = N_2$.

levels for the B groups, and an initial increase in albumin for the C groups, followed by a general decrease for all groups by day 3. The day-7 levels for all groups were lower than the corresponding baseline values but, for all groups other than B_1 and C_2, were higher than the corresponding day-3 values.

A general decrease in sodium levels and a corresponding increase in potassium levels occurred from day 1 to day 7 for all groups. Though some of the tests were significant, the reasons for the significance are not clear.

Clinical parameters

Weight remained essentially the same in the lightly treated drug-control group (A_1). The heavily treated control group (A_2) had a slight but significant weight loss in the 30-day period studied. Animals in irradiated, treated groups (B and C) experienced significant weight losses prior to their deaths (table II). The temperatures were quite variable within the groups, and no significant inference may be obtained (table III).

IV. DISCUSSION

The hematologic response of the drug-control group appears to be that of the ordinary brief reaction to a drug challenge with most parameters returning to the baseline values by the end of the 7-day period investigated. The treated, irradiated animals responded immediately to the challenge with a somewhat similar reaction, then gradually reacted in the typical manner of animals sustaining radiation injury. The eventual lack of survivors among the protected animals confirmed the absence of mobilization of physiologic mechanisms for defense against the radiation insult (3).

The blood chemistry response in both drug controls and treated, irradiated animals was similar, with the exception of the direct portion of the bilirubin which increased more lastingly in the drug controls. Elucidation of the reasons for this difference requires further investigation. This finding agrees with previous studies (2) which found degenerative changes in liver and kidneys of primates dying of toxic effects of WR-1607.

Of the clinical parameters, the change in weight appeared to be the only contributory factor, conforming to the general response to a chemical challenge and typical subacute radiation syndrome.

One may conclude that WR-1607, as utilized in this experiment, failed to effectively mobilize physiologic mechanisms for protection against the radiation injury. All treated, irradiated animals responded in the typical manner to the ionizing radiation as determined by the parameters evaluated. Further investigation of this drug as a potential radioprotective agent must consider a different approach to its administration.

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Jose A. Martinez-O'Ferrall, Major, USAF, MC
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13. ABSTRACT

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